REMARKS

Title Amendments

The title has been amended to delete reference to "apparatus," as requested by the Examiner.

Specification Amendments

The specification has been amended to inactivate a hyperlink, as requested by the Examiner.

Claim Amendments

Claims 1, 3, and 35-57 are now pending in the application. Claims 1 and 3 have been amended; claims 35-57 are new.

Support for claim 35 can be found, for example, at page 7, lines 15-16. Support for claim 36 can be found, for example, at page 8, lines 15-16; page 8, lines 1-5; and Figure 1. Support for claim 37 can be found, for example, at page 12, lines 16-23; and page 18, line 22 to page 19, line 3. Support for claim 38 can be found, for example, at page 8, lines 18-22 and page 14, lines 2-6. Support for claims 39-40 can be found, for example, at page 9, lines 1-4; and page 13, lines 7-13. Support for claim 41 can be found, for example, at page 13, lines 13-15. Support for claims 42-43 can be found, for example, at page 8, lines 22-24; and page 13, lines 16-21. Support for claim 44 can be found, for example, at page 8, line 24 to page 9, line 1; and page 13, lines 2-5. Support for claim 45 can be found, for example, at page 14, lines 10-17. Support for claim 46 can be found, for example, at page 14, lines 5-9. Support for claim 47 can be found, for example, at page 14, lines 10-17. Support for claims 48-49 can be found, for example, at page 16, line 21 to page 17, line 7. Support for claim 50 can be found, for example, at page 15, line 13 to page 16, line 8. Support for claims 51-54 can be found, for example, at page 16, lines 8-20. Support for claim 55 can be found, for example, at page 17, line 22 to page 18, line 4. Support for claims 56-57 can be found, for example, at page 19, lines 3-7.

No new matter has been added. Reconsideration and reexamination are respectfully requested in view of the amendments and the following remarks.

Objections

The Examiner objected that the title is not descriptive because the claimed invention is directed to a method while the title recites method and apparatus. The applicants have amended the title to recite method but not apparatus. The applicants submit that the title as amended is clearly indicative of the invention to which the claims are directed.

The Examiner also objected that the disclosure contains an embedded hyperlink and/or other form of browser-executable code. The applicants have amended the specification to inactivate the link, as per MPEP § 608.01. The applicants submit that the disclosure is now proper.

Withdrawal of the objections is requested.

Lack of Enablement Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1 and 3 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner acknowledges that the specification enables a computer implemented method for predicting the structure of the membrane bound protein bacteriorhodopsin (BRDP) and six named olfactory receptors. But the Examiner says that the specification does not reasonably provide enablement for a computer implemented method for predicting the structure of any membrane-bound protein because protein crystallization is unpredictable. The applicants respectfully disagree.

No undue experimentation is required to implement the claimed computer implemented methods. The claimed methods do not recite, require, or otherwise rely on structural data from X-ray crystallography, which can be time consuming and expensive and does not work for some proteins (Specification, page 3, lines 18-21; page 19, lines 21-24). Rather, the claimed methods rely on the amino acid sequence for the membrane-bound protein which, together with two molecular dynamics simulations, is used to output a predicted structure for the membrane-bound protein. Amino acid sequences are easily determined (Specification, page 19, lines 11-16) and the disclosure is sufficient to enable a skilled artisan to configure the computer to possess the requisite functionality, i.e. output a predicted structure for a membrane-bound protein having a

plurality of helical regions. Accordingly, the applicants respectfully submit that the claimed methods are enabled for any membrane-bound protein having a plurality of helical regions.

The evidence as a whole, as demonstrated by a consideration of the Wands factors, clearly supports this conclusion. *In re Wands*, 858 F.2d 731, 737, 740 (Fed. Cir. 1988). First, the quantity of experimentation need to practice the invention is very small, as the molecular dynamics simulations upon which the invention relies are fully operational and generally known to those of skill in the art. Second, the amount of direction presented in the specification is fully adequate to enable one of skill in the art to practice the invention because the specification clearly describes how these known simulations are used to implement the invention.

Third, the applicants include two complete and distinct working examples, one of which involves application of the claimed invention to six different proteins.

Fourth, the nature of the invention is not experimental laboratory biology but rather computer-implemented modeling, in particular, modeling of molecular dynamics. Such methods are reliably implemented to yield definite results. Fifth, the prior art is well-developed and very sophisticated, as indicated for example by the number and quality of the references in the specification. Sixth and similarly, the relative skill of those in the art is quite high. Such persons are knowledgeable of computer coding techniques, mathematical methods, and protein structure and function. Seventh and as suggested above, the art of computer modeling is not an unpredictable science but, rather, a very deterministic one.

Eighth and finally, the breadth of the claims are consistent with and fully supported by the specification. Thus, the evidence as a whole indicates that it would not require undue experimentation to practice the claimed invention. Accordingly, the applicants respectfully submit that the specification is enabling with respect to the claimed invention.

The applicants also respectfully submit that the scope of enablement is not properly limited to those proteins for which the accuracy of the prediction methods is known. A primary purpose of the applicants' claimed methods is to predict the tertiary structure of membrane-bound proteins for which expensive and difficult X-ray crystallographic studies are not available.

This purpose is demonstrated by the fact that the applicants' predicted BRDP structure compares reasonably well with the crystallographic BRDP structure.

In addition, the calculated binding energies for the predicted OR S25 structure showed good correlation to the measured recognition profiles for two known odorants of OR S25, as discussed in Example 2. No X-ray crystallographic data was available for this protein.

Similarly, Rose et al. (U.S. Patent No. 5,680,319) presents predicted and observed structural data only for cytochrome b562, but claims a computer implemented method for predicting the three-dimensional structure of any protein fragment. Limiting the scope of the applicants' claims to proteins whose structure has been determined both empirically and by the claimed methods would negate the purpose of the invention and is inappropriate when, as here, one skilled in the art can practice the claimed invention in light of applicants' disclosure.

Accordingly, the applicants respectfully submit that the claimed methods are fully enabled by the specification, and should not be limited in scope to the examples described in the specifications or to proteins whose structure has been determined both empirically and by the claimed methods. Withdrawal of the rejection is requested.

Claim Rejections 35 USC § 103

The Examiner rejected claims 1 and 3 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,680,319 ("Rose") taken with Kyte et al., 1982 ("Kyte").

Rose describes a method that predicts a three-dimensional structure for a fragment of a protein by first repeatedly randomly selecting and then testing conformations for each of several predefined intervals of amino acids, then fixing any conformation that is commonly selected for an interval, and thereafter repeating the process with the fixed conformations for successively larger sequential intervals. The testing of a conformation depends on steric overlap and estimations of attractive forces, while the fixing of a conformation depends on the frequency with which it occurs in the repeated selections.

In contrast, the claimed invention predicts the complete structure of a membrane-bound protein by first identifying transmembrane regions and optimizing a helix bundle configuration

in one molecular dynamics simulation, then constructing inter-helical loops to generate a full-atom model and optimizing the full-atom model in another molecular dynamics simulation – not just incrementally testing intervals of amino acids for any of several conformations until the structure of a fragment has been defined. Thus, the claimed invention differs from the teachings of Rose in many significant ways.

The Examiner acknowledged that Rose does not disclose predicting the structure of a membrane-bound protein, but says that Kyte teaches such a method. The applicants respectfully disagree. Kyte describes a method for evaluating hydropathy along an amino acid sequence and using that information to infer the location of portions of the sequence in the folded protein. Kyte uses the method to identify membrane-spanning segments of a protein, or amino acids that are likely to be on the exterior or interior of a protein. Kyte does not, however, describe or suggest a method for predicting the structure of a membrane-bound protein.

Nonetheless, and even if Kyte provides motivation to apply Rose's method to predicting the structure of a membrane-bound protein, the present invention is patentable over Rose and Kyte because neither reference describes or suggests the sequential use, as in the claimed invention, of a first molecular dynamics simulation for a set of helices and a second molecular dynamics simulation for a full-atom model. That is, neither reference describes or suggests "optimizing a helix bundle configuration for the set of helices using a first molecular dynamics simulation" and then, "after optimizing the helix bundle configuration, constructing one or more inter-helical loops to generate a full-atom model of the membrane-bound protein" and "optimizing the full-atom model using a second molecular dynamics simulation".

Importantly, neither Rose nor Kyte teach or suggest "optimizing a helix bundle configuration for the set of helices". First, neither teaches or suggests "a set of [constructed] helices for the transmembrane regions" whose configuration can be optimized. Rose teaches selection and possible fixing of a conformation, i.e. a portion of a helix or strand, a turn, or part of a coil, for the sequential intervals. But each interval is predefined by the method, its conformation can be fixed as one of several conformations, and the outputted fragments can include all conformations. Thus, Rose describes a method for assigning any of several

conformations to predefined intervals – but does not describe or suggest a method of constructing helices for ranges of amino acids in the amino acid sequence identified as transmembrane regions, as required by the claimed invention. Kyte simply does not teach or suggest the construction of helices.

Second, even if Rose and/or Kyte taught "a set of [constructed] helices for the transmembrane regions", neither teaches or suggests "optimizing a helix bundle configuration for the set of helices using a first molecular dynamics simulation". Rose applies its described method to a protein that happens to have a four helix bundle, and outputs a protein structure in which the orientation of three of these four helices compares favorably to data from x-ray crystallography studies (See Rose column 8, lines 13-24, and Figures 7a-c). But Rose does not optimize just the helix bundle, independently of other portions of the protein. Rather, Rose simulates predefined fragments of the protein including possibly all types of conformations, and then outputs a structure which happens to include a set of helices. Kyte addresses the location of hydrophobic or hydrophilic residues, as in a transmembrane region, but does not use a molecular dynamics simulation and does not optimize a helix bundle configuration. Thus, neither Kyte nor Rose describes or suggests optimizing a helix bundle configuration as required by the present invention.

Moreover, even if Rose and/or Kyte describe optimization of a helix bundle configuration, neither teaches or suggests "optimizing [a] full-atom model using a second molecular dynamics simulation" where the full-atom model was generated by "constructing one or more inter-helical loops" *after* optimizing the configuration of a helix bundle. Rose describes a method that evaluates the conformation of successively larger intervals of an amino acid sequence. But as discussed previously, those intervals are not identified as transmembrane regions, are not constructed as helices, and are not configured into an optimal arrangement. In addition, even if they were, Rose does not add inter-helical loops to an already optimized helix bundle configuration. Rose also does not optimize a full-atom model. Rose's method is limited to determining the conformations of protein *fragments* – not a full protein, including all of its atoms (See, e.g., Rose column 4, lines 42-48; column 11, lines 35-37). And while Rose's method uses

sequentially larger intervals, there is no first and second simulation as required in the claimed invention. In short, neither Rose nor Kyte teach or suggest the use of a second molecular dynamics simulation to optimize a full atom model that is generated by adding inter-helical loops to the optimized configuration of a helix bundle, as required in the claimed invention.

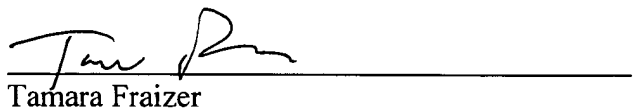
For any and all of these reasons, the applicants respectfully submit that claim 1 is allowable. Claim 3 and new claims 35-57 depend from claim 1 and are allowable at least for any of the reasons given for claim 1. Withdrawal of the rejection is requested.

In summary, reconsideration and withdrawal of the Examiner's objections and rejections are respectfully requested. Early allowance of the claims of this application is earnestly solicited.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: March 2, 2004



Tamara Fraizer
Reg. No. 51,699

Fish & Richardson P.C.
500 Arguello Street, Suite 500
Redwood City, California 94063
Telephone: (650) 839-5070
Facsimile: (650) 839-5071

50196180.doc